

In the Claims:

1 - 109. (Cancelled)

110. (Currently amended) A method of analysing fluorescence emitted by radiation excited samples in an array of samples, comprising the steps of:

focusing light emitted from each sample using objective lenses ~~arranged below the sample array~~ so as to form parallel beams from samples making up the array;

subsequently focusing the parallel beams through a single point and locating at the single point an aperture to filter out light which is not emanating from one of the focal points of the objective lenses;

re-establishing a parallel array of light beams by the use of an additional lens so as to present ~~to an addressable charge coupled detector array~~ a plurality of parallel beams corresponding to the beams from the samples;

gathering the plurality of parallel beams using optical fibres, which map the beams onto an addressable charge coupled detector array;

individually addressing different regions of the detector array onto which the beams impinge, to determine the light incident thereon; and

storing data relating to the quantity of incident light on each said region of the detector array together with address information to enable the data to be reconciled with the position of the sample in the array to which that data relates,

in which a shutter is provided to inhibit the transfer of light to the detector array, excitation radiation is supplied for an interval of time and then shut off, after a selected interval of time the shutter ~~preventing~~ inhibiting transfer of light to the detector array is opened, and after an integration interval, the residual charge pattern on the detector array is interrogated to generate a signal relating to the charge pattern for processing and storage as aforesaid.

111. (Previously presented) A method according to claim 110, further comprising the steps of: introducing periodically excitation radiation and projecting same onto a specific region in each sample; and

thereafter extinguishing the excitation radiation and enabling fluorescence caused by the excitation to pass through the same optical devices to emerge as parallel beams for

transfer to the detector array.

112. (Previously presented) A method of imaging a plurality of micro-samples simultaneously onto separately addressable detectors so that light emitted from each micro-sample is monitorable by one of the detectors, the method comprising the steps of:

locating a corresponding plurality of objective lenses adjacent to the micro-samples with one objective lens for each micro-sample, the latter being located at or near the focal point of each of the lenses so that light emanating from each micro-sample is collected by its respective objective lens and converted into a beam of parallel or near parallel rays, the objective lenses being arranged so that the beams issuing therefrom are parallel; and

focusing the beams by a focusing lens through a single point and collecting the beams beyond that point by detector lens means which serve to reconstitute the parallel beams for presentation to the detectors,

in which a pinhole is placed at the focal point of the focusing lens to filter out light which is not emanating from the focal point of each of the objective lenses, wherein a filter is located in front of the detectors, and apertured masks are placed on either side of the filter to collimate the parallel beams to further reduce background and cross-talk.

113. (Previously presented) A method according to claim 112, wherein the axes of the objective lenses are angled.

114. (Previously presented) A method according to claim 112, wherein the focusing lens is a multi-component lens employed for directing the beams through the single point.

115. (Previously presented) A method according to claim 112, wherein the micro-samples are positioned relative to the objective lenses so that the region of interest is as close as possible to the focal point of the respective objective lens.

116. (Previously presented) A method according to claim 112, wherein the micro-samples are located on a planar support with the regions of interest in the same plane, and the objective lenses are located in a common plane parallel to that containing the regions of interest in the micro-samples.

117. (Previously presented) A method according to claim 112, including the step of:
adjusting the positions of the micro-samples relative to the lenses; and
individually adjusting the positions of at least the objective lenses relative to the micro-samples or vice versa so that the regions of interest in the micro-samples are at the focal points of the respective objective lenses.
118. (Previously presented) A method according to claim 112, wherein in order to provide spectral separation based on wavelength, a filter is included in the light path either between the micro-sample objective lenses and the focusing lens means ahead of the pinhole, or between the detector lens and the detector array.
119. (Previously presented) A method according to claim 118, wherein the filter is located in a region in which the light paths are parallel or nearly parallel.
120. (Previously presented) A method according to claim 112, wherein fluorescence generates the radiation which is to be focused onto a detector, and excitation radiation to produce the fluorescence is applied only to a region of interest within each micro-sample rather than over the whole of the micro-sample.
121. (Previously presented) A method according to claim 120, wherein excitation radiation is injected so as to proceed in a parallel sense towards the array of objective lenses, in an opposite sense to the light which emanates from the micro-samples, so as to be focused by the objective lenses onto the region of interest in each micro-sample.
122. (Previously presented) A method according to claim 121, wherein the excitation radiation is injected as a parallel beam into the optical path, at right angles thereto, onto a 45° beam splitting device, from which it is directed as a parallel beam towards the objective lenses, and radiation from the micro-samples can pass through the beam splitting device to the focusing lens.
123. (Previously presented) A method according to claim 112, wherein excitation radiation is produced using a laser, and a beam expander is employed to expand the cross-section of the laser beam into an area equivalent to the area of the array of objective lenses.

124. (Previously presented) A method according to claim 112, having an 8 x 12 array of objective lenses on the same 8 x 12 matrix as a standard 96 well plate, wherein a well plate is moved using an XY stage relative to the array of objective lenses so as to present groups of 96 wells to the 96 lens array.

125. (Previously presented) A method according to claim 112, wherein the parallel beams of light directed towards the detectors are transferred thereto via optical fibres, in the form of a fibre optic bundle or fibre optic plate.

126. (Previously presented) A method according to claim 125, wherein a bundle of fibres is employed, the arrangement of the fibres in the bundle differing between the input and output ends thereof so that the shape of the output end of the bundle conforms to the shape of the detector array in the XY plane.

127. (Previously presented) A method according to claim 112, wherein the detectors are in a charge coupled device having separately addressable regions.

128. (Previously presented) A method according to claim 127, wherein the charge coupled device is cooled.

129. (Previously presented) A method according to claim 112 wherein the detectors comprise an array of photomultipliers, one photomultiplier for each beam.

130. (Previously presented) A method according to claim 129, wherein each photomultiplier has a window, and optical fibres are employed to convey the light from each of the apertures in a mask to the windows of the photomultipliers, which together occupy an area greater than that of the mask.

131. (Previously presented) A method according to claim 129, wherein the photomultipliers are gated electronically.

132. (Previously presented) A method according to claim 112, wherein the detectors are in the form of an image intensifier or an intensified CCD.

133. (Previously presented) A method according to claim 132 wherein the image intensifier or intensified CCD is gated electronically.

134. (Previously presented) A method according to claim 112, wherein additional lenses for focusing the parallel beams of light directed towards the detectors are employed to improve resolution at the detector surface either alone or in combination with a fibre optic transfer bundle.

135. (Previously presented) A method according to claim 112, wherein micro-lenses, optionally in combination with a fibre optic transfer plate, are employed in the objective lenses adjacent the micro-samples.

136. (Previously presented) A method according to claim 135, in which the micro-lenses have one infinite conjugate.

137. (Previously presented) Apparatus for imaging a plurality of micro-sample light emitting sites simultaneously, comprising:

means for supporting a micro-sample array on a substrate parallel to an array of objective lenses arranged so as to correspond on a one-to-one basis with the positions and spacing of at least some of the micro-samples, each of the objective lenses having a focal length and being positioned relative to a region of its related micro-sample at a distance equal to the focal length of the lens so that light emitted from that region of the micro-sample will emerge from the lens as a parallel beam parallel to the axis of the lens, and the parallel beams of light are focused by means of a single focusing lens onto a detector lens so as to produce an image of the micro-sample light emissions in a plane of an array of individually addressable photoelectric detectors;

a pinhole aperture at the focal point of the focusing lens to filter out light which is not emanating from one of the focal points of the objective lenses from reaching the detectors;

shutter means to inhibit the passage of excitation light from a light source, except when required for excitation purposes; and

additional shutter means synchronised with that associated with the light source to prevent light reaching the detectors whilst excitation light is projected into the system,

wherein a filter is located in front of the detectors;

apertured masks are placed on either side of the filter to collimate the parallel beam to reduce background and cross-talk;

circuit means are provided to which signals read out from the detector array are supplied, each signal corresponding to the light incident on a region of the detector array for a given period of time from one of the micro-samples; and

computing and analysing circuit means are provided, responsive to the electrical signals, together with memory means for storing values indicative of the light emitted from each of the micro-samples together with detector array address information, whereby each stored value is identifiable with the respective micro-sample.

138. (Previously presented) Apparatus according to claim 137, further including:

a beam splitter interposed in the optical path between the objective lenses and the focusing lens to enable light to pass from the lenses to the focusing lens, and to enable excitation radiation to be reflected as a parallel beam towards the objective lenses, thereby utilising the optical focusing characteristics of the objective lenses to focus the parallel light into spots of light which register with the micro-samples.

139. (Previously presented) Apparatus according to claim 137, including a laser source as the source of excitation radiation, and a beam expander for enlarging the cross-section of the laser beam and presenting a beam of excitation radiation for entry into the imaging system via the beam splitter.

140. (Previously presented) A method of imaging an array of micro-samples simultaneously onto separately addressable detectors so that light emitted from each micro-sample is monitorable by one of the detectors, comprising the steps of:

locating a corresponding plurality of objective lenses adjacent to the micro-sample array, with one objective lens for each micro-sample, the latter being located at or near the focal point of each of the lenses so that light emanating from each micro-sample is collected by its respective objective lens and converted into a beam of parallel or near parallel rays, the objective lenses being arranged so that the beams issuing therefrom are parallel;

focusing the beams with a focusing lens through a single point;

collecting the beams beyond that point by detector lens means which serve to reconstitute the parallel beams for presentation to the detectors;

placing a pinhole at the focal point of the focusing lens to filter out light which is not emanating from the focal point of each of the objective lenses;

providing an array of 96 micro-lenses positioned so as to image each region down on a spot of small size at the surface of the detectors; and

providing a beam splitter in the optical path between the objective lenses and the focusing lens to enable light to pass from the lenses to the focusing lens, and to enable excitation radiation to be reflected as a parallel beam towards the objective lenses, thereby utilising the optical focusing characteristics of the objective lenses to focus the parallel light into spots of light which register with the micro-samples.

141. (Previously presented) Apparatus for imaging a plurality of micro-samples simultaneously, comprising:

means for supporting a micro-sample array on a substrate parallel to an array of objective lenses arranged so as to correspond on a one-to-one basis with the positions and spacing of at least some of the micro-samples, each of the objective lenses having a focal length and being positioned relative to a region of its related micro-sample at a distance equal to the focal length of the lens so that light emitted from that region of the micro-sample will emerge from the lens as a parallel beam parallel to the axis of the lens, and the parallel beams of light are focused by means of a single focusing lens onto a detector lens so as to produce an image of the micro-sample light emissions in the plane of an array of individually addressable photoelectric detectors;

a pinhole at the focal point of the focusing lens to filter out light which is not emanating from one of the focal points of the objective lenses from reaching the detectors;

shutter means to inhibit the passage of excitation light from a light source except when required for excitation purposes;

an array of 96 micro-lenses positioned so as to image a region of each micro-sample down on a spot of small size at the surface of the detector;

a beam splitter interposed in the optical path between the objective lenses and the focusing lens to enable light to pass from the lenses to the focusing lens, and to enable excitation radiation to be reflected as a parallel beam towards the objective lenses, thereby utilising the optical focusing characteristics of the objective lenses to focus the parallel light into spots of light which register with the micro-samples;

additional shutter means synchronised with that associated with the light source to prevent light reaching the detectors whilst excitation light is projected into the system;

circuit means to which signals read out from the detector array are supplied, each signal corresponding to the light incident on a region of the detector array for a given period of time from one of the micro-samples;

computing and analysing circuit means, responsive to the electrical signals; and

memory means for storing values indicative of the light emitted from each of the micro-samples together with detector array address information, whereby each stored value is identifiable with the respective micro-sample.

142. (Previously presented) Apparatus according to claim 141, further including filter means provided in the optical path between the beam splitter and the detector array to substantially prevent excitation radiation from reaching the detector array.

143. (Previously presented) Apparatus according to claim 141, including a laser source as the source of excitation radiation, and a beam expander for enlarging the cross-section of the laser beam and presenting a beam of excitation radiation for entry into the imaging system via the beam splitter.

144. (Currently amended) A method of imaging a plurality of micro-samples simultaneously onto separately addressable detectors so that light emitted from each micro-sample is monitorable by one of the detectors, comprising the steps of:

locating a corresponding plurality of objective lenses adjacent to the micro-sample array, with one objective lens for each micro-sample, the latter being located at or near the focal point of each of the lenses so that light emanating from each micro-sample is collected by its respective objective lens and converted into a beam of parallel or near parallel rays, the objective lenses being arranged so that the beams issuing therefrom are parallel;

focusing the beams with a focusing lens through a single point;

~~collecting the beams beyond that point by detector lens means which serve to reconstitute the parallel beams for presentation to the detectors; and~~

placing a pinhole at the focal point of the focusing lens to filter out light which is not emanating from the focal point of each of the objective ~~lenses, lenses;~~

~~wherein the detector array comprises an array of photomultipliers, one photomultiplier for each of the optical paths.~~

collecting the beams beyond that point by detector lens means which serve to reconstitute the parallel beams; and

gathering the parallel beams using optical fibres, which map the beams onto the detectors.

145. (Currently amended) Apparatus for imaging a plurality of micro-samples simultaneously, comprising:

an array of objective lenses;

means for supporting a micro-sample array on a substrate parallel to ~~an~~the array of objective lenses, the objective lenses being arranged so as to correspond on a one-to-one basis with the positions and spacing of at least some of the micro-samples, each of the objective lenses having a focal length and being positioned relative to a region of its related micro-sample at a distance equal to the focal length of the lens so that light emitted from that region of the micro-sample will emerge from the lens as a parallel beam parallel to the axis of the lens;

~~lens, and~~ a focusing lens for focusing the parallel beams of light are focused by means of a single focusing lens onto a detector lens so as to produce an through a single point;
~~image of the micro-sample light emissions in the plane of an array of individually addressable photoelectric detectors;~~

a pinhole aperture at the focal point of the focusing lens to filter out light which is not emanating from one of the focal points of the objective lenses from reaching the detectors;

a detector lens for collecting the beams and reconstituting the parallel beams;

optical fibres for gathering the parallel beams and mapping them onto an array of individually addressable photoelectric detectors;

shutter means to inhibit the passage of excitation from a light, except when required for excitation purposes;

additional shutter means synchronised with that associated with the source to ~~prevent~~ inhibit light of any wavelength reaching the detectors whilst excitation light is projected into the system;

circuit means to which signals read out from the array are supplied, each corresponding to the light incident on a region of the detectors for a given period of time from one of the micro-samples;

computing and analysing circuit means, responsive to the electrical signals; and

memory means for storing values indicative of the light emitted from each of the micro-samples together with detector array address information, whereby each stored value can be identified with the respective ~~micro-sample array~~, micro-sample.

~~wherein the detector array comprises an array of photomultipliers, one photomultiplier for each of the optical paths.~~

146. (Previously presented) Apparatus according to claim 145, further including a beam splitter in the optical path between the objective lenses and the focusing lens to enable light to pass from the lenses to the focusing lens, and to enable excitation radiation to be reflected as a parallel beam towards the objective lenses, thereby utilising the optical focusing characteristics of the objective lenses to focus the parallel light into spots of light which register with the micro-samples; and

filter means in the optical path between the beam splitter and the detector array to substantially prevent excitation radiation from reaching the detector array.

147. (Previously presented) Apparatus according to claim 145, including a laser source as the source of excitation radiation, and a beam expander for enlarging the cross-section of the laser beam and presenting a beam of excitation radiation for entry into the imaging system via the beam splitter.

148. (Previously presented) A method of measurement of radiation from a plurality of sample sites, wherein a plurality (N) of single channel confocal optical systems and photoelectric detectors or detecting areas are arranged in parallel to form a plurality of reading heads arranged side-by-side so as simultaneously to read a corresponding plurality of adjacent sample sites, wherein the reading heads are independently adjustable so that each is accurately positionable over or under a sample site.

149. (Previously presented) A method according to claim 148, wherein the sites are arranged in an array, and the optical systems are arranged in a single line for reading

column by column a multi-column array, or in a staggered pattern for simultaneously viewing sites in different columns.

150. (Previously presented) A method according to claim 148, using (N) independent confocal systems, each with its optic axis aligned with one sample site.

151. (Previously presented) A method according to claim 148, wherein light from a single laser source is split into a plurality of beams, each conveyed by a fibre optic cable to an individual sample site.

152. (Previously presented) A method according to claim 148, wherein light emitted from the separate sites is conveyed to individual detectors, or discrete regions of an array detector, via optical fibres.

153. (Previously presented) A method according to claim 148, wherein an opto-mechanical device is provided to bring each optical system into alignment with a respective site.